Aus der Urologischen Abteilung
des Inselspitals Bern
Dir. Prof. Dr. E. Wildbolz

A CLINICAL REEVALUATION OF THE THIOSEMICARBOZONES

Inaugural-Dissertation
zur Erlangung der Doktorwürde
der Medizinischen Fakultät
der
Universität Bern

vorgelegt von
MICHAEL WAINSTON
aus New York

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A Clinical Reevaluation of the Thiosemicarbozones

The results of the test series run by the Veterans Administration in the U. S. with the drug TB I led them to discontinue its clinical use. They found that the toxic side effects prevented the further administration of TB I in the treatment of tuberculosis. Dr. John K. Lattimer of the Veterans Administration discussed this problem with Dr. E. Wildbolz.

Dr. Wildbolz using Tebacyl, a similar structural compound to TB I, had found a much smaller percentage of toxic side effects at the urological Sanatorium at Leysin. The percentage of side effects were so minimal at Leysin, that they were a striking contrast to the Veterans administrations series. The aim of this paper is, therefore, to compare these results in the use of TB I and Tebacyl as therapy in tuberculosis.

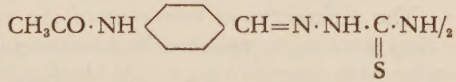
The success of sulfonamide in combating streptococcal infection led its way into the treatment of tuberculosis. *Wildbolz* as early as 1941 reported a strong healing influence of sulfonamide upon tuberculosis and non-specific fistulas. He reported a specific effect upon granulation building besides the long known influence on the metabolism of the bacteria.

Domagk and his coworkers, the chemists *Behasch*, *Mietzsch* and *Schmidt* found after many experiments Sulfathiodiozal and especially Benzaldehyde-Thiosemicarbozone, a stepping stone in the synthesis of Aminothiodiozal to Sulfathiodiozal, to have very promising tuberculostatic effects.

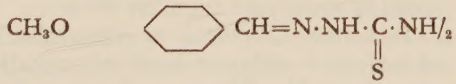
They systematically tested hundreds of sulfonamides for the tuberculostatic effects in vitro and found, that the Thiazolring and not the Sulfonamide character of these drugs were responsible for the tuberculostatic effect.

From Benzaldehade-Thiosemicarbozone three compounds were developed:

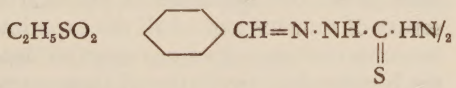
TB I / 698 Conteben
Benthozon, TBK



TB II / 242



TB III / 1734



TB II and TB III were not as compatible as TB I and therefore TB I under the name of „Conteben" received thorough experimental and clinical tests.

Hirt and Hurni completed many animal experiments and a comparison of the results of TB I 698 and Tebacyl shows:

	Tuberculostat. effect — 10 g. Mol	Toxicity MLD by Mouth Mg/Kg
TB I / 698	4.1	4000
Tebacyl	5.6	6000

The absorption and excretion rates of TB I and Tebacyl in vivo were not found to be markedly different. On the other hand, the toxicity tests by Hirt and Hurni have given interesting results. Acute toxicity in rats, guinea pigs and mice have shown a somewhat lower toxicity for Tebacyl than for TB I in all three kinds of animals under apparently identical conditions of absorption and excretion.

The acute toxicity tests in rabbits were performed with a restricted number of animals. They gave the following preliminary results upon peroral administration.

Preparation	Dose Mg/Kg	Death Rate	Symptoms
1057 H	20	0/2	none
(Tebacyl)	50	0/2	none
	100	0/4	none
	200	0/2	none
	400	1/2	tendency to spasms, oedema of the lungs transudate
1016 H TB I	20	2/4	oedema of the lungs polyserositis, pulmonary

The differences in tolerance of the two preparations are very striking. They cannot be explained by admitting lack of absorption of 1057 H, since even with doses as high as 100 Mg/Kg, from 40 to 60 % of the applied dose could be recovered from the urine.

To better understand the remarkable apparently species bound variation of toxicity in different kinds of animals, protein binding power of serum were done. No difference of practical value could be found between the serum of humans and of all the experimental animals. Therefore, the difference in tolerance does not seem to depend on the physical, but rather on the biochemical properties of these compounds.

As *Lindner* stated in his paper, the Thiosemicarbozone (TSC), dependent on the dosage, had a decided inhibitory effect on the course of the tubercu-

lous infection of the experimental animals. The dosage to be effective for TB I was 150 Mg pro Kg. In the control animals which were not treated with TSC, they showed the typical tubercle arrangement with giant cells, epitheloid cells and nekrosis plus *Ziehl-Nielsen stained tubercle bacillus*. Those animals treated with TSC after the same observation time, showed non of the specific changes. These results were only obtained with the high dosage of TSC.

Hurni showed through many experiments the effects of the TSC in influencing the course of tuberculosis. The good effect on the course of tuberculosis of TSC are not only described as a tuberculostatic, but as many authors feel, it has an effect on the body itself. As a possibility of the indirect influence, *Heilmeyer* describes an effect similar to cortisone. He also described a detoxifying effect of TSC on tuberculin.

Brondtner and *Svoboda* also showed the detoxifying effect on the Morosalve. The reaction with the addition of TB I was neither blocked or weakened. *Heck* and *Frautwein* also included TB I in the tuberculin test on animals with a higher doses of TB I, they had similar results as *Brondtner* and *Svoboda* in the experiments with Morosalve.

Concerning the mechanism of action of the Thiosemicarbozones, almost nothing definite is known (Heilmeyer, Hurni). It may be considered certain however that, besides their tuberculostatic activity, non-specific effects play an important role, chiefly in connection with immunologic processes. A specific antagonism to other substances, such as between P-Amino Salicylic and P-Aminobenzoic Acid, doses not exist apparently.

One of the main problems of treatment with TSC is due to the relatively small difference between the tuberculostatic and toxic dosage. In comparative studies on the tuberculostatic activity in vitro, *Hirt* and *Hurni* have shown Tebacyl to be superior to the other Thiosemicarbozones. That for instance it is about 10 × more active than TB I. The absorption and excretion rates in vivo were not found to be markedly different from those of related compounds. On the other hand, the toxicity tests Hirt and Hurni have shown Tebacyl to be less toxic for most laboratory animals than TB I.

In 1949 *Steinlin* conducted a series with TSC on 100 patients and used both TB I and Tebacyl:

„After having checked the subjective and objective tolerance of this preparation during several months, which required many laboratory tests, we began treatment of two parallel series of patients. One serie receiving P-Acetylaminobenzaldehyde TSC, the other a new TSC derivative-test preparation 1057 Wander Tebacyl; this latter has been shown in vitro and in the animal to be as active as TB I, while its toxicity proved to be somewhat lower".

Lindner divided the side effects of TSC into three groups:

1. Primary Toxic Symptoms
2. Allergic Manifestations
3. Toxic – Allergic late Symptoms

Under the first group are the symptoms which appear after high dosage of TSC: loss of appetite, nausea, vomiting. They are attributable to a stimulus of the stomach mucosa. Through longer administration a stimulus to the vagus ganglion may play a role. Usually though an adjustment to the drug takes place and the symptoms of the nausea complex disappear.

Symptoms which become manifest under the second group were exanthema, erythema, urticaria. These symptoms were usually of short duration. Those skin irritations which became very chronic, either disappeared with a reduction, or upon complete cessation of therapy. Mild leucopenia and seldom agronulocytosis were also observed. During the TB I treatment, a pronounced sensitivity to pyramidon was observed. *Heilmeyer* reported cases of agranulocytosis through the TSC-pyramidon therapy. *Klee* reported one case of urobilinogenuria and subicterus in the course of TSC therapy.

A toxic-allergic late symptom was the change in the erythrocytes to the „*Stechapfel*" form. *Lindner* feels that TSC is not very toxic, but its side effects are greater than Pas. *Steinlin's* views on TSC and Tebacyl as result of his 100 patients series are: „As far as the side effects are concerned, we have seen occasionally a slight deterioration of appetite, with the use of TB I. We observed quite frequently a decrease in Haemoglobin at the beginning of treatment; however, with the administration of iron the Haemoglobin content of the blood was soon normalized without discontinuing medicine. In one case we observed a more serious Anaemia with preparation 1057 (Tebacyl). The initial drop of Haemoglobin was less severe and other side effects were extremely rare. Therefore, this drug may be qualified as less toxic in man also".

Test series using TB I under the auspices of the Veterans Administration was carried out in the U. S. The regimen of therapy was starting with 50 Mg by mouth daily for the first week, 100 Mg daily the second week, 200 Mg by mouth daily for the third and ensuing weeks. What follows is a survey of 250 Patients treated under this regimen of the Veterans Administration and a comparison of the results obtained in Leysin, Switzerland.

Skavlem, ed al. reported on the results of 63 patients treated with TB I (P-Acetyl-Aminobenzaldehyde-Thiosemicarbozone). They found that due to toxicity, the drug was stopped on 26 patients: „Toxic reactions were encountered in most of the patients. In 26 patients treatment was discontinued because of toxicity to the drug. In the remaining individuals toxic symptoms were so mild and transient, that they did not interfere with treatment."

„Anorexia, nausea and vomiting were encountered in 32 patients. This necessitated stopping treatment in 15 white male patients. Since 13 of these men were in the same ward, and since the symptoms were usually mild in patients in other wards, we believe that the severity of symptoms in the white males had a large psychic component."

Skavlem reports further that anaemia was the commonest serious complication. He found a drop in Haemoglobin and in the Erythrocyte count

to below the pre-treatment levels in almost all cases treated. Skavlem reports that with the administration of liver extract and iron some improvement was noted, but in no case did the blood return to normal. Anaemia was classified as severe in five patients (below 10 grams % HB or below 3 million RBC).

He also reported one case of severe liver damage. In three cases of known diabetics one became difficult to control with insulin soon after taking TB I. Another patient not previously known to be a diabetic developed severe diabetes. A third diabetic required no change in diet or insulin dosage.

The toxic reactions as compiled on the 63 patients at the Dunham Hospital:

Anorexia, nausea, vomiting	32
Liver damage	1
Abdominal pain	3
Conjunctivitis	3
Skin rash	2
Fever	1
Anaemia mild	18
medium	17
severe	5

As was stated by Skavlem in the summation of his paper: „The maintenance dose of 200 Mg daily may be somewhat in excess of necessary dose and studies of 100 or 150 Mg daily are recommended“. . . .

In another series run under the Veterans Administration at Baylor University College of Medicine, *Sandhaus*, *Halpert*, *Burdon* and *Jenkins* reported on 21 patients receiving Tibione alone or in combination. The report states:

„The doses used and the method of administration were those recommended by the committee on therapeutic agents of the Veterans Administration. The initial dose of Tibione was 50 Mg administered daily during the first week. The dose was then increased by 50 Mg weekly until the full dose of 200 Mg per day was reached by the beginning of the fourth week. This dose was continued until 120 days of therapy were completed. Thus, each patient who completed the course of treatment received 14.7 grams of Tibione.“

The side effecas in this series of 21 patients are:

Anorexia, nausea, vomiting	9
Granulocytopenia	1
Haemolytic anaemia	2
Depression of RBC and HB	1

Renal impairment:

5 patients who were treated with Tibione alone developed evidence of renal disturbance during treatment as shown by an increase in the blood

urea nitrogen or by the appearance of albumin and red blood cells in urine or both.

Renal impairment	Tibione alone	5
Renal impairment	Tibione and Strepto	4
Hepatic impairment	Tibione alone	6

9 patients in a series of 21 had to discontinue therapy due to the toxic symptoms that developed.

Another series run on 15 patients at the VA Hospital at Hines, Illinois, using the same treatment regimen was reported by *Shemoslin*, *Desautels*.

Their report states:

„Manifestations of toxicity attributable to Tibione under daily dose of 200 Mg were reported at one time or another in 12 of 15 patients of this series".

Anorexia, nausea, vomiting	10	discontinuation	2
Changes in liver function text	6		
RBC count reduced 500000 per M.1.	7		
RBC count reduced 1 million	2		
WBC reduction	2		
Renal irritation	5		

Only 5 patients completed the therapy as Tibione was discontinued on 10 patients due to toxic symptoms.

Dr. *Dressler* report under the same regime.

26 patients were treated at National Jewish Hospital:

Side reactions	–
Conjunctivites	5
Nausea	3
Mild Diarrhea	3
Generalized rash	1
Agronulocytosis	2

This series showed 14 toxic symptoms in 26 patients. Yet another series reported by Tempel of a total of 65 patients under same therapy regimen:

„Of the 65 patients studied to date 38 or 59% have shown toxicity. In 12 or 19% of them the toxicity was sufficient to require discontinuance of the drug".

Gastro-intestinal	34	discontinuation	9
Liver damage	12	discontinuation	8
Depression	11		
Skin eruption	3		
Transient conjunctivitis	2		

A series run by *Murphy* on 16 patients had some interesting results. He did not follow the 200 Mg dosage but decreased it to 100 Mg. 14 cases were considered to have a long enough period to have had an effect on the organism. Only *one* of the 14 patients had any evidence of toxicity and none showed blood changes.

In contrast to the almost constant high % of toxic symptoms found in all the series run in the U. S., with the drug TB I (Tibione) small % of toxic symptoms were found in the series conducted at Leysin with the drug Tebacyl. Dr. Hoess and I worked through all the case histories at the Station d'Urologie at Leysin and compiled the statistics concerning Tebacyl and its side effects.

In this series conducted by *Wildbolz*, 56 patients received Tebacyl therapy at the clinic in Leysin. Of the 56, 21 received Tebacyl alone and the rest received Tebacyl in combination as listed below:

1.	Tebacyl,	Rimifon	4
2.	„	Pas	9
3.	„	Rimifon, Strep.	1
4.	„	Hydrochaul. Pas	2
5.	„	Hydrochaul. Strep.	2
6.	„	Strep. Vide	1
7.	„	Hydrochaul. Vide	2
8.	„	Pas, Rimifon	2
9.	„	Hydrochaul.	9
10.	„	Vitamin d_2	3

The amount of Tebacyl received by each varied from 67 tablets to 410. The dosage regimen followed here is the one prescribed by Wander:

„Clinical experience has shown the full therapeutic effect of Tebacyl is obtained with relatively small doses. Early symptoms can be avoided best with small progressively increasing doses. The treatment is usually started with 25 Mg daily. During the second week dosage is received to 25 Mg twice daily; during the third week to 25 Mg three times daily and from the fourth week on the full daily dose of 50 Mg twice daily is given. The daily requirement of 100.Mg of Tebacyl is exactly half of what was given in the U. S. after the gradual increase in four weeks time".

3 of the 56 patients treated with Tebacyl had to have the drug discontinued. Two for reasons of nausea and vomiting and one because of depression of the Haemoglobin. One other patient complained of anorexia and nausea, but the symptoms passed quickly without interruption of therapy. Another 2 patients showed a depression of the white blood cells count, but this also passed without interruption of therapy.

Case I

M. J. ♀, 1902 TBC Renalis Bilateralis, Hydropyonephrosis. Patient's Haemoglobin and red blood cells count were checked before therapy.

After therapy with Tebacyl the Haemoglobin began to fall, it went from 80% to 65% Haemoglobin in 3 weeks – non protein nitrogen remained high – Leucocytes remained within the normal range.

Fe therapy combined with Tebacyl did not alter the depression of Haemoglobin. After continued therapy Haemoglobin fell to 50% with corresponding reduction of red blood cells. Tebacyl was discontinued because of this severe reduction of the Haemoglobin and RBC. Haemoglobin and RBC count then slowly returned to normal after some weeks without Tebacyl.

Case II

K O 1922 – Tuberculosis of the residual left kidney

This patient showed the symptoms of anorexia, nausea and vomiting. The symptoms began after months of Tebacyl therapy. It was noted after symptoms began, that the patient was taking an overdosage of Tebacyl himself. Patient was observed and reinstated on regular regimen of drug. There was no way to determine the exact amount or duration of the overdosage. No Haemoglobin or white count reduction were noted. Non protein nitrogen remained within normal range on repeated tests during the stage of anorexia and nausea.

Case III

L.K. $\underset{+}{0}$ Condition after left nephrectomy stenosis of ureter

This patient at a tuberculosis clinic in Germany showed a sensitivity to Conteben. A discontinuance of the administration of Conteben had to be taken due to the severe nausea and vomiting that developed. At Leysin, the patient was free of toxic effects with tebacyl for 2½ months. Then the patient developed the symptoms of anorexia, nausea and vomiting. Therapy had to be stopped and the symptoms cleared promptly.

Case IV

A.M. 0 1914 Status after Nephrectomy of left residual kidney, Epididymectomy, TBC of right kidney

Patient was receiving Tebacyl in combination with Hydrochaulmoophtiol and Streptomycin. Patient was on therapy for 6 months when he developed an intolerance to the drug in the form of nausea and vomiting. Tebacyl was reduced to 1 tablet a day with no decided change. As Tebacyl was completely discontinued, the signs of nausea and vomiting disappeared.

Side effects:

Anorexia, nausea, vomiting	3	discontinued therapy	2
Haemoglobin reduction	1	„ „	1
Leucopenia	2		

The two cases of Leucopenia showed depression of the white blood cells, count to 4100 and 3100. Therapy was not discontinued and the white count again climbed to within the normal range. Of the 56 patients receiving

Tebacyl alone or in combination only 3 had to discontinue therapy due to toxic symptoms.

Case II shows that the toxic symptoms, only in combination with an overdose of Tebacyl, became manifest.

Case III shows that the patient had earlier been sensitive to Conteben and after 2½ months therapy with Tebacyl, again showed the same toxic effects.

The results of the TB I series conducted in the U.S. has shown an extremely high rate of toxicity. In many cases as much as 80%, therapy had to be stopped due to the toxic effects. The dose in almost all the cases was 200 Mg per day after the third week of therapy was reached. In one series where the dose was dropped to 100 Mg after the appearance of toxic effect, all the patients were able to complete the 3 months course of therapy.

In the test series of 100 cases using both Tebacyl and TB I. *Steinlin* stated that he rarely increased dosage to 150 Mg per day and never exceeded this dosage. Thus, he remained within the therapeutic range and had low toxic side effects. His paper reads:

„As far as side effects are concerned, we have seen occasionally a slight deterioration of appetite. With the use of P-Acetyl-Aminobezaldehyde-Thiosemicarbozone we observed quite frequently a decrease in Haemoglobin at the beginning of treatment; however with the administration of iron the Haemoglobin content of the blood was soon normalized without discontinuing medication".

Steinlin has shown further, that using small doses of TB I a relatively small amount of toxic symptoms will become manifest. The results at Leysin have shown, that with a maintenance dosage of 100 Mg a day of Tebacyl, the toxic effects were much lower than any of the American reports. At Leysin only in 5% of the patients were the toxic effects severe enough to cause a termination of the therapy. The American reports showed 30, 60% and even 80% termination of therapy due to toxic effects. Tebacyl has shown itself to be clearly less toxic than TB I. It has also been used successfully in combined therapy with Rimifon, Pas and Streptomycin. Tebacyl has also been successfully used alone as post operative therapy over long periods of time (one to two years). It is easily administered and lends itself well for home therapy. With the clinical evidence gained at Leysin, Tebacyl should replace TB I in the therapy of tuberculosis and should be made an active member in the fight against TBC.

Bibliography

1. Preparation 1057 „Wander", a new Tuberculostatic agent belonging to the group of the Thiosemicarbozones.
2. Tuberkulostatische Wirkung und Toxizität einiger Thiosemicarbozone, von R. Hirt und H. Hurni. – Schweiz. Zeitschrift für Allgemeine Pathologie und Bakteriologie. Separatum Vol. XIII, Fasc. 4 (1950).
3. Die therapeutische Bedeutung der Thiosemicarbozone bei tuberkulösen Infektionen, von Dr. A. Lindner, Wien. Subsidia Medica 1950, Heft 2.
4. Zum Wirkungsmechanismus der Thiosemicarbozone, von Hans Hurni. – Schweiz. Zeitschrift für Tuberkulose, Vol. IX. Fasc. I., 1952.
5. Versuche der Behandlung banaler und tuberkulöser Fisteln mit Sulfanilamidpräparaten, von Egon Wildbolz. Beiträge zur Klinik der Tuberkulose Bd. 97, Heft 1.
6. Tebacyl-Wander.
7. On the Chemotherapeutic treatment of Cavitary lung tuberculosis with thiosemicarbozones. Schweiz. – Zeitschrift für Tuberkulose, 1950.
8. Transactions of the 10th conference on Chemotherapy of tuberculosis (Streptomycin conference) January 1951 Veterans Administration Army, Navy.

a) Thiosemicarbozones in Tuberculosis. Report of treatment in 63 cases. John H. Sklavem M.D.; Harold I. Humphrey, M.D.; Robert W. Whing, M.D.; Ruth P. Sprinkle, M.D.

b) Tibione treatment of Pulmonary Tuberculosis, a pilot study. Harold S. Sandhaus, M. D.; Bela Halpert, M. D.; Kenneth L. Bardon, Ph. D.; and Daniel E. Jenkins, M. D.

c) Tibione in the treatment of Pulmonary Tuberculosis. Arnomld Shomosken, M. D.; Eugen J. Desautels, M. D.; James R. Zvelna, M. D.; George S. Berg, M. D.

d) Mematologic effects of TB I (Tibione). Abraham Falk, M.D. and Leslie Ziene M.D.

e) Further Clinical Experience with Amithozone (Tibione). Solomon Netzer, M.D.; Joseph A. Schwartz, M.D. and John D. Davies, M.D.